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REVIEW

The clinical impact of cytomegalovirus infection following allogeneic hematopoietic cell transplantation: Why the quest for meaningful prophylaxis still matters

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ABSTRACT

Latent infection with human cytomegalovirus (CMV) is common. Functional immunity effectively contains such latent infections; however, CMV reactivation may cause significant complications in patients undergoing allogeneic hematopoietic cell transplantation (alloHCT). In spite of the universal implementation of post-transplant screening for CMV viremia and the institution of pre-emptive antiviral management, CMV disease still occurs in a small portion of patients. Moreover, interactions between CMV and the immune system have significant implications for the incidence of graft-versus-host disease, the recurrence of malignancy, and non-relapse mortality following alloHCT, even in the era of pre-emptive antiviral management. CMV serostatus thus remains an important consideration for patients undergoing alloHCT. We review the clinical impact of CMV in the setting of alloHCT, interactions between CMV serostatus, viral reactivation, and transplant outcomes, as well as current and evolving strategies for prevention and treatment of CMV-related complications that may have significant impact for alloHCT recipients.

1. Introduction

Primary human cytomegalovirus (CMV) infection commonly occurs in childhood, and the immune system of infected individuals thereafter sustains continuous suppression of viral replication. In patients undergoing allogeneic hematopoietic cell transplantation (alloHCT) or solid organ transplantation (SOT), this important suppressive immunity is temporarily lost or attenuated, leading to the reactivation of viral replication and dissemination between different tissues. Due to recent advances in CMV detection and treatment strategies, the incidence of CMV disease (i.e., symptomatic end-organ infection) has decreased, but not been eliminated, in patients undergoing alloHCT and SOT. In alloHCT, the standard approach to CMV management in the post-transplant setting is to initiate pre-emptive antiviral therapy upon detection of significant viremia, whereas it is more common to administer prophylactic antiviral therapy following SOT. The difference in strategies between alloHCT and SOT is primarily driven by the ability of most SOT patients to tolerate myelosuppression associated with the most commonly used antiviral agents, valganciclovir and ganciclovir, whereas myelosuppression is undesirable in the early post-alloHCT setting [1]. In spite of pre-emptive management of CMV reactivation/infection, CMV-seropositive patients continue to experience poorer outcomes than CMV-seronegative patients through increased non-relapse morality and decreased overall survival [2,3].

Attempts to standardize methods for CMV genome quantification in alloHCT recipients have yielded quantitative PCR assays associated with high intralaboratory consistency; however, interassay and interlaboratory results may still vary by ten-fold (1 $\log_{10}$), while efforts to harmonize an international standard remain ongoing [4]. CMV disease, though rare since the implementation of these strategies, still occurs, and can unfortunately be quite devastating. Recognition of CMV disease, which may occur without detectable viremia, remains important for alloHCT patients. Due to the deleterious impact of CMV infection on alloHCT outcomes, new strategies for preventing and controlling CMV reactivation in transplant recipients remain a crucial goal of several lines of clinical investigation. Strategies with promise include the development of better tolerated pharmacologic inhibitors of viral replication, as well as immunologic approaches including monoclonal antibodies, vaccines, and cellular therapies for CMV.

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2. Clinical manifestations of CMV

2.1. CMV viremia and organ disease

CMV reactivation, or secondary infection, occurs when CMV replicates within an individual and virus-derived nucleic acids or proteins become detectable in the body fluids or tissues, generally as a consequence of immune suppressive therapy [5]. The incidence of CMV reactivation is roughly 50% (reported range 40–80%) in CMV-seropositive alloHCT recipients not receiving anti-viral prophylaxis (i.e., most alloHCT recipients) [6–12]. In addition, roughly 30% of CMV seronegative recipients of grafts from seropositive donors also develop primary CMV infection [6], which is clinically indistinguishable from CMV reactivation in seropositive recipients. CMV viremia may be asymptomatic or accompanied by constitutional symptoms such as pyrexia; however, reactivation is most frequently diagnosed in the absence of symptoms during routine surveillance after alloHCT. CMV viremia is now commonly quantified by quantitative PCR (Q-PCR), but the conversion to this technology occurred within the past 10 years, and some institutions will have recently used bloodborne CMV antigen (pp65) quantification.

CMV disease, defined as the isolation of CMV from an appropriate tissue specimen along with clinical signs and symptoms of compatible end-organ dysfunction [5], may manifest in various organs, sometimes with fatal complications. When treated with pre-emptive antiviral therapies, <5% of cases with CMV reactivation progress to CMV disease [13]. High initial viral load (>20,000 copies/mL) in blood correlates with the likelihood of CMV disease ($P = 0.008$), as does the presence of leukopenia (white blood cell count < 3000/mL) at CMV viremia diagnosis (HR 4.347, 95%CI 1.33–14.25, $P = 0.045$) [14]. Furthermore, refractory CMV infection, defined as CMV viremia lasting greater than two weeks despite anti-CMV treatment, occurs in half (50.6%) of patients experiencing CMV viremia, and is associated with increased risk for CMV disease (HR 10.539, 95% CI 2.467–45.015, $P = 0.001$) and treatment-related mortality (HR 8.435, 95% CI 1.511–47.099, $P = 0.015$) when it occurs within the first 100 days [15]. In the setting of refractory CMV infection, the toxicities of prolonged treatment that may contribute to negative outcomes include myelosuppression, renal impairment, and in rare instances, multi-drug resistant CMV disease [16–20].

It is worth noting that in spite of broad usage of sensitive Q-PCR detection of viremia, some patients are found to have CMV organ disease without antecedent or concurrent viremia — GI infection and retinitis being particularly associated with this phenomenon [21]. This is likely due to effective immune-mediated viral control outside the affected organ, and may lead to under-diagnosis or delayed treatment for CMV disease. There is, however, a downward trend in the incidence of fatal CMV disease, likely attributable to the increased sensitivity of diagnostic methods and improved efficacy of preventive and treatment strategies [22,23].

2.2. The spectrum of CMV organ infections

CMV interstitial pneumonitis or pneumonia, which was the most common form of symptomatic CMV infection in the post-transplant setting prior to the advent of pre-emptive treatment strategies, remains the most lethal of CMV organ infections, and is diagnosed when CMV is identified in bronchoalveolar lavage (BAL) fluid or lung tissue accompanied by pulmonary compromise [5]. The mortality rate associated with CMV pneumonitis is >50% [21,24,25]. This high-risk infection presents with hypoxia, dyspnea, fever, cough, and, in some instances, pleural effusions, and may be coincident with other pulmonary infections. Ultimately, CMV pneumonitis may lead to respiratory failure [5], and patients suffering this complication often require intensive care unit (ICU) admission with rigorous ventilatory support [22].

CMV gastroenteritis and/or colitis, characterized by a combination of the presence of CMV in the gastrointestinal (GI) tract, macroscopic mucosal lesions, and an array of clinical symptoms that vary depending on the location of involvement within the GI tract, is a potentially fatal end-organ infection for which the mortality rate is difficult to define. The diagnosis and treatment of CMV gastroenteritis is complicated by the fact that GI graft-versus-host disease (GVHD) and GI CMV disease share nearly identical clinical presentations, including symptoms such as abdominal pain, secretory diarrhea, and sometimes bloody stools. Additionally, these two clinical entities may also occur simultaneously post-alloHCT [26]. Both CMV antigenemia and viral load screening tests appear to have limited value in predicting the onset of CMV gastroenteritis, as GI CMV disease may be diagnosed before CMV is detectable in the peripheral blood [27,28].

Less frequently, CMV disease may affect other organs such as the eyes and components of the central nervous system. CMV retinitis is diagnosed by ophthalmoscopic findings of necrotic retinal lesions, sometimes accompanied by retinal hemorrhage, along with isolation of CMV in the peripheral blood [5,29–31]. The apparent late onset of CMV retinitis is due to its mostly asymptomatic nature, where patients do not experience visual symptoms such as blurred vision and retinal floaters until more advanced stages of disease. In addition, because CMV retinitis is often accompanied by other post-alloHCT complications such as GVHD and multi-organ CMV infection, its diagnosis may be delayed or even missed. Only eleven cases of CMV meningoencephalitic disease were reported in the literature from 1950 to 2008, illustrating the rarity of this end-organ infection, although it is possible some CNS infections go unrecognized [32]. CNS CMV presents as encephalitis and is defined by the presence of CNS symptoms accompanied by the detection of CMV in the CSF, brain biopsy, or by culture. Unlike CMV retinitis, patients with CNS CMV do not generally experience other sites of CMV disease. A recent survey identified a CMV encephalitis incidence rate of 0.7% amongst 281 alloHCT recipients [33].

Although hepatic sinusoidal epithelial cells are a primary site of latent CMV reactivation in murine models [34], CMV hepatitis has only rarely been described in the alloHCT population. It is likely that hepatic CMV infection is under-diagnosed due the relative infrequency of liver biopsies pursued in this setting [35]. CMV hepatitis has been better described in liver transplant recipients, where the threshold for liver biopsy is lower, suggesting other patients undergoing post-transplant immune suppression may be subjected to similar phenomena [36]. As with GI CMV disease and GVHD, hepatocellular inflammation in the setting of hepatic CMV disease may be associated with hepatic GVHD.

Other organs that may be affected by CMV disease include the kidneys, bladder, heart, pancreas, and gallbladder, though such tissue infections are uncommon [5].

3. Interplay between CMV and post-transplant outcomes

3.1. Relationship between CMV and graft-versus-host disease

Graft-versus-host disease is a complication of alloHCT in which donor immune cells recognize recipient cells as foreign, triggering an immune response against the recipient's healthy tissues. GVHD is frequently associated with impaired post-transplant quality of life and is a major cause of mortality and morbidity. Based on existing literature, the relationship between CMV and GVHD is best described as bidirectional: in most instances, GVHD increases the risk of CMV infection, and in other instances, CMV infection is associated with the onset.

In one of the earliest studies of the relationship between CMV and GVHD, Miller and colleagues found that CMV and acute graft-versus-host disease (aGVHD) were strongly associated, where aGVHD preceded identification of CMV infection by a median 34 days [37]. Immunosuppressive corticosteroids used to treat aGVHD and the immunosuppressive effects of aGVHD itself may permit reactivation of latent virus, increasing the risk of CMV replication in seropositive patients. While modern methods of CMV screening were not yet available at the time, likely delaying the time to diagnosis of CMV infection after